A Research proposal

"DESIGN AND DEVELOPMENT OF NANOBIOCOMPOSITES FOR LIFE STYLE DISEASE UTILIZING QBD APPROCH"

Submitted to

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1. INTRODUCTION

1.1 INTRODUCTION TO NANOBIOCOMPOSITE

Nanoparticles have gained more attention in recent years due to their potential properties such as small size, high surface to volume ratio and high tumor penetration.The properties of Nanoparticles such as conductivity, optical and mechanical properties are different than bulk material although composition of material is same.

Nanobiocomposites can be defined as multiphase materials, where one or more of the phases consists of at least one dimension less than 100 nm. The properties of nanocomposite materials depend on the properties of their individual parents, their morphology and interfacial characteristics.

The term nanobiocomposite includes a wide range of materials right from three dimensional metal matrix composites, two dimensional lamellar composites and nano-wires of single dimension to zero-dimensional core-shells all representing many variations of nano-mixed and layered materials. The physical, chemical and biological properties of nano materials are different from the properties of individual atoms and molecules or bulk matter.

It is possible to control the fundamental properties of materials, such as their melting temperature, magnetic properties, charge capacity and even their colour without changing the material's chemical compositions by creating nanoparticles. Thus, nanobiocomposites promise new applications in many fields such as mechanically reinforced lightweight components, battery cathodes, nano-wires, non-linear optics, sensors and in drug delivery as carriers. Inorganic layered materials exist in many varieties. They posses well defined, ordered intralamellar space potentially accessible by foreign species. This ability enables them to act as matrices for polymers yielding hybrid nanocomposites.

Nanobiocomposites are classified into three types:

a) Nano layered composites: Which are composed of alternating layers of nanoscale dimension.
b) Nano filamentary composites: Which are composed of matrices with embedded (generally aligned) nanoscale diameter filaments.

c) Nano particulate composites: These are composed of matrices with embedded nanoscale particles. By engineering the polymer-host interactions, nanocomposites could be prepared with the broad range of properties.

Lamellar nanocomposites can be divided into two classes such as intercalated and exfoliated. In the former, the polymer chains are alternately present with the inorganic layers in a fixed compositional ratio and have well-defined number of polymer layers in the intralamellar space.

Nanobiocomposite – Basic ingredients:

over the last few years, there has been a great deal of interest in polymer nanocomposites. There are different types of commercially available nano-particles that can be incorporated into the polymer matrix to form polymer nanocomposites. The correct selection of particle is essential to ensure effective penetration of polymer or its precursor into the interlayer spacing of the reinforcement and result in the desired exfoliated or intercalated product. Polymer nanocomposites are consist of polymeric materials with reinforcement of nano-particles. Polymer could incorporate either as the polymeric species itself or via the monomer, which is polymerized in situ to give the corresponding polymer-clay nanocomposite. Most commonly used nano-particles include:

- Nanosilica (N-silica)
- Montmorillonite organoclays (MMT)
- Carbon nanofibers
- Carbon nanotubes
- Nanoaluminum oxide (Al_2O_3)
- Nanotitanium oxide (TiO_2)

There are two main challenges in developing nanocomposite materials after the desired polymer has been selected for the purpose. First, the choice of nano-particles requires an interfacial interaction and/or compatibility with polymer matrix. Second, the processing technique should address proper uniform dispersion and distribution of nano-particle aggregates within thepolymer matrix.

1.1.1 IDEAL PROPERTIES OF NANOBIOCOMPOSITE

- It should have high surface to volume ratio for loading of biomolecules.
- It should have high mechanical strength.
- It should have high electrical conductivity.
- It should have high environmental stability.

1.1.2 IDEAL PROPERTIES OF DRUG TO BE USED NANOBIOCOMPOSITE

- The material should have flexibility, high thermal and mechanical nature.
- The smart properties like the stimuli-responsive character.
- The material should have adjustable dimension, multifunctional property and highbiocompatibility.
- The material should have good dispersion capability.
- The material should have more surface area.
- The material should have stability.

1.1.3 IDEAL PROPERTIES OF POLYMER TO BE USED NANOBIOCOMPOSITE

- The polymer should improve the stability of the nanobiocomposite.
- The polymer should improve the mechanical property (strength, elastic modules anddimension stability) of the formulation.
- The polymer should improve the permeability of the drug.

1.1.4 METHOD FOR PREPARATION OF NANOBIOCOMPOSITE

- Solution intercalation method
- Emulsion/solvent evaporation method
- Melt intercalation method
- Emulsification solvent diffusion method
- Double emulsion solvent evaporation method
- Film casting method
- Electrospinning method
- Co- precipitation method
- Ionic interaction method
- Microwave- induced diffusion
- Ultrasonication method

The various investigations show that nanobiocomposite proved to be beneficial as a drug delivery system such as enhanced antiemetic activity, intrathecal delivery in gene therapy, colon cancer treatment, antibacterial and antifungal activity, control release delivery of anticancer drug paclitaxel, drug delivery injectable cell scaffold in tissue engineering, and remote control drug release.

1.2 OBESITY

"Overweight or obesity is a multifactorial disease and major risk factor for many chronicdiseases, including diabetes mellitus, cardiovascular diseases, and cancer. Previously, Obesity was considered a health issue in developed countries, but now it is common worldwide, particularly in urban areas. There are many etiologic factors for this, which includes genetic, metabolic, behavioural, and environmental variables. The rapid increase in the prevalence of overweight suggests that behavioural and environmental influences are predominant, rather than biological changes.

Obesity is considered a chronic metabolic disorder that enables the advent of multiple other metabolic disorders such as cardiovascular diseases, type 2 diabetes, fatty liver disease, and certain cancers. Obesity is further associated with dyslipidemia which includes elevation in serum total cholesterol, triglyceride (TG), and low-density lipoprotein (LDL)-cholesterol and demotion of high-density lipoprotein (HDL)-cholesterol. Obesity develops as a result of hypertrophy and/or hyperplasia of adipocytes which occures due to the differentiation of pre-adipocytes through adipogenesis.

Fig.1 : Obesity and associated risk factors

There are two parts of the obesity equation:

(1) an increased intake of foods with large amounts of fat, salt, and sugars, but less vitamins, minerals and other nutrients; and

(2) Due to lifestyle changes a decrease in physical activity , changing modes of transportation, irregular daily routines and increasing urbanization.

Thus, the fundamental cause of obesity and overweight is an energy imbalance between calories consumed and calories expended. The body needs a certain amount of energy, or calories, from food to sustain basic life functions. Body weight is maintained when daily calories eaten are equals those used. When more calories are consumed than those burned, the overall energy balance is tilted toward weight gain, predisposing one towards being weight gain and possibly obese.

Due to the high morbidity and mortality, the management and treatment of obesity requires numerous resources which includes pharmacologic agents, balanced diets, and physical exercise.

Five distinct mechanisms or strategies for weight loss:

1) Reducing food intake either by augmenting the inhibitory effects of anorexigenic signals or factors that reduces food intake or by blocking orexigenic signals or factors that stimulate food intake.

2) Blocking nutrient absorption in the alimentary canal, particularly absorption of fat.

3) Increasing thermogenesis by uncoupling fuel metabolism from the ATP generation, thereby dissipating food energy as heat.

4) Modulating fat and protein metabolism or storage by regulating fat synthesis/lipolysis or adipose differentiation /apoptosis. Increased fat or protein turnover might reduce body weight by affecting either food intake or energy expenditure.

5) Modulating the central controller regulating body weight by- (1) changeing the internal reference value sought by the controller or (2) modulating the primary afferent signals regarding fat stores analysed by the controller. This approach would have the potential advantage of forcing the endogenous controller to maintain multiple pathways of energy balance and minimize restitution.

Drugs commonly used to control obesity are categorized as follows:

- Serotonergic agents: dexfenfluramine, fluoxetine, fenfluramine.
- Noradrenergic agents: phendimetrazine, phentermine, amphetamine, diethylpropion, pseudoephedrine, phenylpropanolamine, mazindol.
- Noradrenergic and Serotonergic agents: sibutramine.
- Drugs acting on the gastrointestinal system: orlistat (pancreatic lipase inhibitor)

- Centrally acting drugs (anorectic or appetite suppressants): sibutramine, rimonabant Suppressive effect on food intake (Promotes feeling of satiety): liraglutide, a glucagon-like peptide-1 analogue (incretin mimetic), exenatide (analogue of the hormone GLP-1), pramlintide (synthetic analogue of the hormone Amylin).

The anti-obesity products in the market can be classifified into three categories:

(1) food ingredients;

(2) herbal ingredients; and

(3) other functional supplements.

Developing functional products from what people usually consume in their daily life is probably the most popular segment in the functional supplement industry. Products made from fruits (citrus, and berries), grains (soybean), vegetables or beverage drinks (tea leaves) are relatively safer and more acceptable to consumers.

Recently, herbal therapies are not only popular in Asia, but also more and more common in the Western world. This is the reason why herbal materials could be another major category of anti-obesity products. Some other materials, e.g., probiotic and calcium supplements, have also been proven to confer anti-obesity effects. Previous studies have explored the potential health benefifits of fruits. The examples of potential health benefifits include anticancer, anti-inflflammatory, and anti-obesity effects.

About 80% world population is dependent on herbal medicines. Herbal drugs are household, easily accessible, without side effects, and used safely from ancient times while modern medicines are not affordable and also have side effects. This increases demand of herbal medicines worldwide. 88% of WHO member states have recognized the importance of traditional medicines.

Obesity is a complex and chronic disorder caused by an interaction of contributing factors, including dietary, lifestyle, genetic, and environmental factors. Appropriate lifestyle and behavior interventions are the fundamentals of weight loss success, but maintaining such a healthy lifestyleis extremely challenging.

The use of some natural anti-obesity products could be considered as a supportive tool to keep obese people holding on their weight-loss goals. It is also possible that the combination of multiple natural products could confer a synergistic activity that increases their anti-obesity action on multiple targets, offering advantages over chemical treatments in terms of serious side-effects. Natural materials may give not only anti-obesity effect but also other health benefifits, such as anti-diabetic and anti-hyperlipidemic activities. It is anticipated that the availability of many natural sources will provide a benefificial basis for developing novel anti-obesity products. Herbal medicinal therapy is the best alternative for overweight or obese people. Thus far, the majority of the various types of remedies developed are chemical or biochemical agents. The purpose of this study was to examine medicinal plants that may be promising alternative treatments in the management and treatment of obesity.

1.3 INTRODUCTION TO QUALITY BY DESIGN

Quality by Design (QbD) is gradually evolving as a advancement of the quality of the product through its life succession. QbD is a considerable change compared to the traditional approach where formulation, design and development typically consisted of univariate experiments which inclues incessant upgrading, revolution in products and processes and also offers increased regulatory flexibility within the design space.

1.3.1 History of QBD

The idea of QbD had initially charted in the 1960s by management counsellor Joseph Juran, who contended that quality should be intentional relatively than just attained in a chaotic way. Previously, Quality was achieved in final product testing and not by process design (QbD) with knowledge of process and formulation variables. The regulatory practice imposed pharmaceutical processes to be operated under the pre-defined and fixed operating conditions irrespective of any sources of variability coming from raw materials or processing conditions.

The FDA's document titled Pharmaceutical cGMPs defined Quality by Design as: 1. Developing product to meet predicted product quality. 2. Scheming manufacturing developments

So, the quality by design based nanobiocomposite drug delivery technology have more opportunity to develop flexible novel herbal dosage form for the treatment of obesity.

The given research proposal is one of the foot step taken to Prepare the Bio-nanocomposite for the management of obesity.

2. REVIEW OF LITRATURE

Liyuan Zhou et. al. (2019) had been reported that, brown adipose tissue (BAT) is highly specialized for the dissipation of energy. Recent evidence indicated that the activation of BAT and the induction of WAT browning might be promising approaches to combat obesity by increasing EE and regulating glucose and lipid metabolism. Resveratrol, which is a polyphenolic compound, has been widely acknowledged to have protective effects against obesity and related metabolic disorders. The induction of WAT browning has been considered as one of the crucial factors in the metabolic benefits of resveratrol. Resveratrolis able to modulate the composition of gut microbiota. In addition, in recent years, the impact of gut microbiota on the browning of WAT has received increasing attention and has been initially confirmed to play a role. This observation might provide novel insights and targets that could be used for fighting against obesity and associated metabolic disorders.

Jens Lund et. al. (2018) he reported that, numerous studies have shown that feeding rodents n-3 polyunsaturated fatty acids attenuates adiposity. The meta-analyses of human dietary intervention studies indicate that fish oil (eicosapentaenoic and docosahexaenoic acid) supplementation might reduce waist circumference. He summarizes that the observations in rodents, highlights several mechanisms that might explain these observations and discusses the translational potential. Given the available in vivo evidence and the ability of human adipocytes to acquire a beige phenotype in response to eicosapentaenoic acid incubation, future studies should test the hypothesis that fish oil activates thermogenic brown and beige adipose tissue in humans. A recent line of research suggests that browning of white adipose depots and activation of uncoupled respiration in brown fat contributes to anti-obesity effect.

Nan-Nong Sun et. Al. (2016) had reviewed on , the anti-obesity effects of different dietary or herbal products, and their active ingredients and mechanisms of action against obesity.

Chowdary et. Al. (2014) had reviewed on QbD to pharmaceutical development by means formulations and manufacturing parameters to deliver pre-targeted quality dosage form. The conception and elements of QbD and its purpose in pharmaceutical product development along with recent research in this area are important in pharmaceutical industry. (Chowdary et al., 2014).

Deshkar et. al. (2013) had dealt with Prednisolone loaded microspheres by gaur gum and HPMC as enteric polymers using QbD approach to deliver drug specifically to colon by combinations of pH dependent and microbial triggered polymers. QbD approach was developed by identifying critical quality attributes (CQA). The independent variables i.e. surfactant concentration and Coat: Core ratio effect on microsphere was optimized on dependent variables by 32 Factorial design. The use of QbD can useful to achieve a better knowledge of product process and formulation variables on microsphere preparation.

Vora et. al. (2013) had studied by varying one factor at a time as preliminary study of carvedilol from transdermal patch. Based on these outcomes, DoE technique was functional followed by regression analysis and response surface methodology to optimize formulation variables. The four formulation variables namely drug loading, matrix thickness, adhesive layer thickness, and propylene glycol concentration was taken to design Central Composite IV model. The 7 hr and 24 hr drug released was used as release response parameters while permeation flux obtained was working as permeation response parameter. All parameters were observed important for release

properties and three of these exhibited significant end product on permeation profile of carvedilol across artificial membrane.

M.G.H. Zaidi et. al. (2012) has prepared iron oxide filled polyvinyl pyrolidone nanocomposite through free radical polymerization reaction using microwave oven. They found that formed nanocomposite may be used as sensor device in magnetic field.

Surendra G. Gattani et. al. (2012) have prepared Microwave-generated bionanocomposite for solubility and dissolution enhancement of poorly water-soluble drug glipizide. It was found that drug distributed as nanocrystalline form in natural polymers & it is concluded that as the concentration of polymer in the composite increased the solubility and dissolution of glipizide were enhanced.

Dumbare et. Al. (2012) had reviewed that optimization is emerged as a technique for the best compromising respond to a particular question. The term optimization is a way to optimize something, or use something at its best. Optimization is finding a ideal, valuable or functional answer. There is no single answer to design optimization tasks. An attempt is made to provide an introduction to the variety of parts and methods which are associated to the optimization techniques such as terms used in optimization, optimization parameters, process of optimization and methods used in the optimization

T.P. Sastry et. al. (2010) Prepared and characterized Nanobiocomposite containing iron Nanoparticle prepared from blood and coated with chitosan and gelatin by precipitation method. They concluded that this Nanobiocomposite may be used as a MRI contrast agent to enhance cellular imaging and as magnetic Nano carrier for targeted. Sarabu Ramana Murthy et. al.

synthesized Tio2 -CoFe2O4 nanocomposite using microwave hydrothermal method. They found that saturation magnetization of samples decreases as with increase of TiO2 content in CoFe2O4.

2.1 REPORTED RESEARCH PATENT ON NANOBIOCOMPOSITE

1. W. Wan, L. Millon patented (Pub. No. US 2009/0028927 A1) "poly vinyl alcohol- bacterial cellulose nanocomposite." They prepared polyvinyl alcohol-bacterial cellulose nanocomposite which is applicable for tissue engineering and control release of bioactive agent.
2. K Makino, H. Terada, T. Nakajima, K. Tomoda (Pub. No. US 2009/0169637 A1) patented "nanocomposite particles." They prepared PLGA-trehalose nanocomposite fordrug delivery. This showed good solubility and good redispersibility when brought in contact with water.
3. A. Guillermo, R. W. Antonio patented (Pub. No. US 2007/0071790 A1) "Biodegradable nanocomposite with enhance mechanical properties for soft tissue." They described method and composition for making and using nanocomposite.
4. J. Bako, S. Marta, J. V. Andrienn, C. Csaba, Z. M. Borbely, H. Csaba, J. Borbely (Pub.No. US 2007/0212419 A1) patented "synthesis of biocompatible nanocomposite hydrogels as a local drug delivery system." They prepared nanocomposite hydrogel asdrug delivery for periodontal infection.

2.2 PLANT PROFILE

Nowadays, traditional Chinese medical practitioners use herbal remedies that usually are combinations of different herbs, such as Moringa Olifera (Drum stick tree/ Miracle tree), Linum usitatissimum (Linseed), Cinnamomum verum (Cinnamon), Coffea arabica (Caffine), Nelumbo nucifera (Lotus leaf with taurine), Blueberry (Vaccinium ashei) and Mulberry (Morus australis), Zingiber officinale (Ginger), turmeric (*Curcuma longa*) and mulberry leaf (*Morus alba*), to treat

obese patients, from above mentioned plants any one or in combination will be used for research activity.

3. AIM AND OBJECTIVE

3.1 AIM

Design and development of nanobiocomposites for life style disease utilizing QbD approch.

3.2 OBJECTIVE

The major objectives of this study are :

- To design and formulate nanobiocomposites of phytoconstituents and their drug delivery system.
- To implement Qbd principle.
- To evaluate prepared nanobiocomposites for antiobesity activity.
- To study optimized nanobiocomposites for *in-vivo* release study.

4. PROPOSED HYPOTHESIS:

- By taking an idea from literature review, we are decided to work on the preparation of nanobiocomposite formulation by using QbD approach.
- Herbal medicinal therapy is the best alternative for overweight or obese people. The purpose of this study was to examine medicinal plants that may be promising alternative treatments in the management of obesity.
- Minimize the several side effects of synthetic drugs and to maximize efficacy of phytoconstituent which are used to combat obesity in novel way.

5. METHODOLOGY :

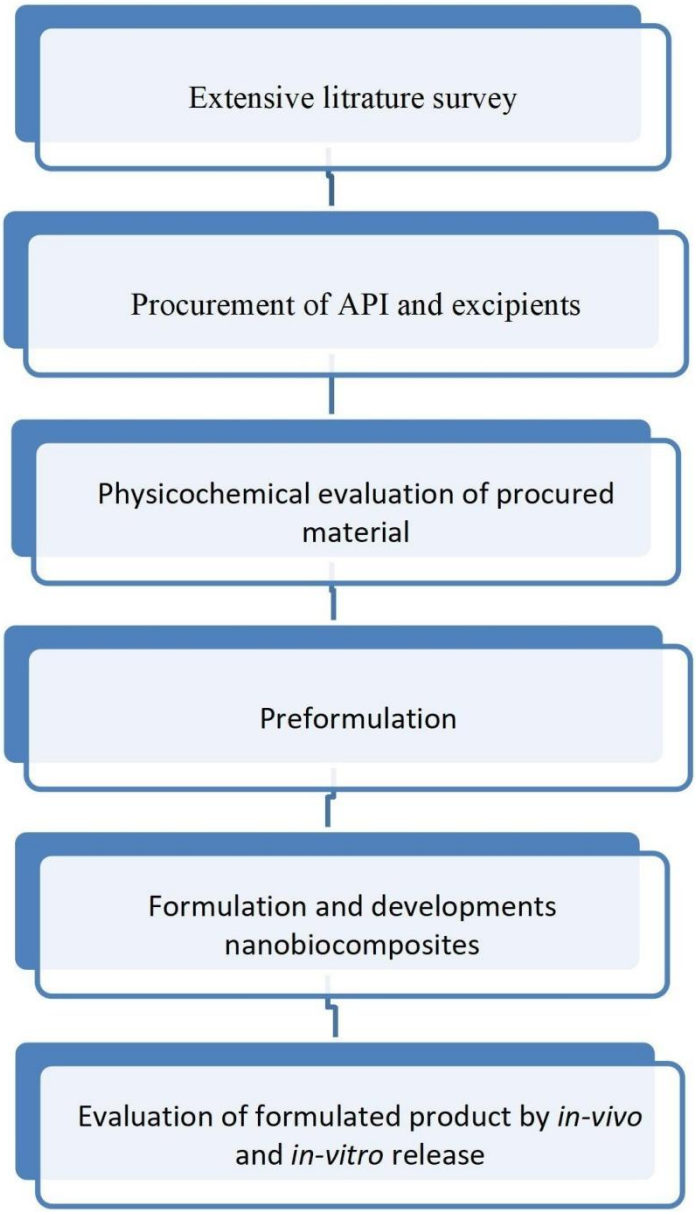
Extensive litrature survey
Procurement of API and excipients
Physicochemical evaluation of procured material
Preformulation
Formulation and developments nanobiocomposites
Evaluation of formulated product by *in-vivo* and *in-vitro* release

Figure. 2: General layout of methodology adopted for research work

6. IMPORTANCE OF THE STUDY:

- Nowadays, People demanding natural products than synthetic, due to its higher safety and efficacy.
- The present study will indicates the importance of QbD approach and its implementation in the preparation and optimization of pharmaceutical product.
- Improve the patient compliance and enhance the effectiveness by formulating nanobiocomposite.

6.1 INTERNATIONAL STATUS :

- In 2016, more than 1.9 billion adults, 18 years and older, were overweight. Of these over 650 million were obese.
- 39% of adults aged 18 years and over were overweight in 2016, and 13% were obese.
- Most of the world's population live in countries where overweight and obesity kills more people than underweight.
- 39 million children under the age of 5 were overweight or obese in 2020.
- Over 340 million children and adolescents aged 5-19 were overweight or obese in 2016.
- Obesity is preventable.

6.2 NATIONAL STATUS :

Obesity levels in India are very high, across all zones. Obesity cases are increasing with age. Obesity is the highest among aging urban men and women who are college educated and are sedentary. Physical activity and aging are the strongest determinants of obesity. Given the high cost of obesity in terms of type 2 diabetes, cardiovascular diseases, and Alzheimer's disease, urgent public health measures are necessary to reduce its impact.

7 RESEARCH WORK PLAN :

Sr. No.	Work	Period
1.	Literature survey	6 months
2.	Procurement of API and Excipients	2 months
3.	Physicochemical evaluation	2 months
4.	Pre-formulation study	3 months
5.	Formulation & Development	6 months
6.	Evaluation of formulated product by in-vitro and in-vivo release study	6 months
7.	Other suggested work and compilation of data	11 months
	Total duration of work	36 month

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